

Single Case

Hemadsorption: A New Therapeutic Option for Selected Cases of Bromazepam Intoxication

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Keywords

Hemadsorption · Blood purification · Intoxication · Bromazepam · Benzodiazepine

Abstract

Benzodiazepine ingestion is frequent in patients admitted to ICU for intoxications. Generally, a supportive approach by securing the airway, breathing, and circulation is sufficient. Flumazenil is a well-known antidote for benzodiazepines but does not influence its elimination. Following preclinical data, we applied for the first time in humans a hemadsorption filter in a patient with a bromazepam intoxication. This technique proved to be effective in eliminating bromazepam in a patient with CHILD-C cirrhosis. We conclude that hemadsorption is a viable option to reduce length of ICU stay or intubation in slow metabolizers without contraindications.

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Introduction

Intoxications account for 1.5–3.7% of ICU admissions [1, 2]. Although the reported mortality in this population is only 2.1%, the cost of hospitalization in ICU for this indication has been calculated at EUR 7,717 per patient [2, 3]. In an epidemiological analysis performed in a tertiary ICU in Edinburgh between 2005 and 2009, the intake of benzodiazepines accounted for 21% of patients admitted with an intoxication, only to be preceded in frequency by alcohol (41%) and tricyclic antidepressants (28%) [4].

Benzodiazepines promote the binding of γ -aminobutyric acid to its receptor, leading to sedative, anxiolytic, anticonvulsant, and muscle relaxant effects. In case of intoxication, a supportive approach by securing the airway, breathing, and circulation is usually sufficient. The required duration of this supportive treatment depends on the half-life of the specific drug [5].

Bromazepam is a lipophilic, intermediate-acting benzodiazepine, with approximately 70% binding to plasma proteins. The drug is metabolized hepatically by CYP enzymes to the pharmacologically active 3-hydroxybromazepam and to 2-(2-amino-5-bromo-3-hydroxy-benzoyl)pyridine. The metabolites are renally cleared after glucuronidation. Bromazepam has an estimated elimination half-life of 10–20 h, which may be longer in elderly patients and in case of hepatic or renal impairment [6].

Flumazenil is a widely known antidote to benzodiazepines. It binds to the γ -aminobutyric acid-A receptor and displaces benzodiazepines in a competitive manner. However, flumazenil has a shorter half-life than most benzodiazepines and does not influence their elimination [5]. A meta-analysis showed that it should not be routinely used in benzodiazepine intoxications, given the potential side effects of seizures and prolongation of the QTc interval, especially in patients with benzodiazepine tolerance or with a history of convulsions [7].

Case Presentation

A 67-year-old woman with CHILD-C liver cirrhosis was admitted to our tertiary ICU after an intoxication with bromazepam. The initial plasma concentration was 874 $\mu\text{g/L}$ (upper limit of normal 170 $\mu\text{g/L}$). The patient developed impending respiratory failure due to a decreased conscious state. Given the expected slow decrease in plasma levels of bromazepam in cirrhosis and the inherent risk of a prolonged need for mechanical ventilation, an infusion of flumazenil was initiated to avoid intubation. The patient regained consciousness and remained stable, but the flumazenil infusion rate could not be decreased due to a relapse of stupor following this intervention.

As expected, only a very slow decrease in bromazepam titer was observed. Based on the decline in titer, the half-life of bromazepam was calculated to be 10 days rather than the expected 10 h. This implied a reduction of the bromazepam titer to 170 $\mu\text{g/L}$ that was only expected after 23 days of ICU admission, warranting a search for further therapeutic options.

Hemadsorption was initiated by applying a Prismax[®] (Baxter, IL, USA) continuous venovenous hemofiltration system combined with a hemadsorption filter (CytoSorb[®]). Sequential quantifications of the bromazepam titer were performed both before and after the hemadsorption filter. These showed that application of a hemadsorption filter was efficient in eliminating bromazepam (–31% after 1 h, –56% after 11 h). After the first 11 h, a quick decline in adsorbing capacity suggested filter saturation (shown in Fig. 1).

No second hemadsorption filter was applied since the upper limit of normal for bromazepam was reached within 1 day of therapy and infusion of flumazenil could quickly be tapered to discontinuation. The patient attained a normal plasma titer of bromazepam 13 days

Fig. 1. Bromazepam concentrations pre- and post-hemadsorption filter over time. Pre-hemadsorption filter concentrations are indicated with triangles and connected with a gray line. Post-hemadsorption filter concentrations are indicated with circles and connected with a black line.

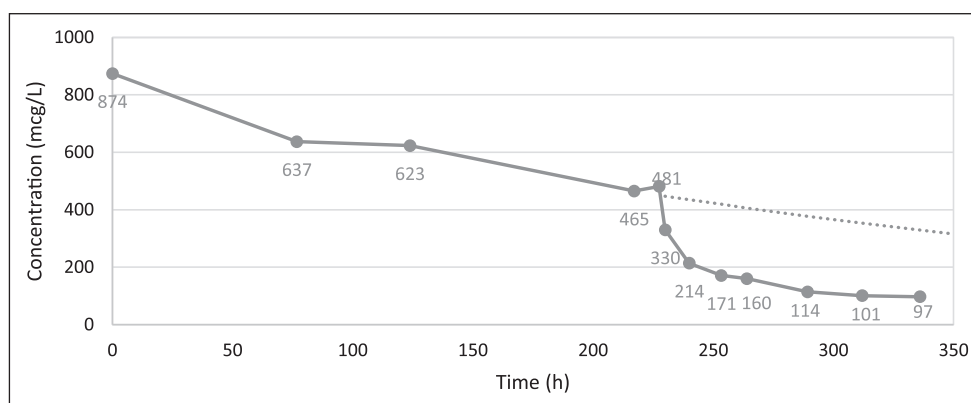
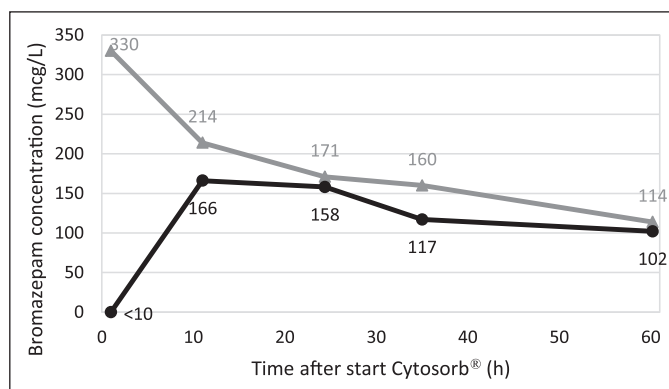


Fig. 2. Plasma concentrations of bromazepam over time. When CytoSorb® was initiated, the plasma concentration of bromazepam was 481 µg/L. The dotted line shows the expected evolution without CytoSorb®.

earlier than predicted without hemadsorption filter. There was no rebound in plasma titer after cessation of the hemadsorption therapy (shown in Fig. 2).

Discussion

To our best knowledge, this is the first report on the use of a hemadsorption filter (CytoSorb®) for a bromazepam intoxication. Hemodialysis, hemoperfusion, and forced diuresis are all known to be inefficient in eliminating benzodiazepines [8]. Hemadsorption on the other hand seems an interesting theoretical option given the lipophilic nature of bromazepam and its molecular weight lower than 60 kDa. The use of hemadsorption in this case was further supported by a small study, presented only as a poster, by Körtge et al. [9] claiming in vitro adsorbability of diazepam when applying a CytoSorb® hemadsorption filter. We think future trials on the use of hemadsorption in intoxicated patients are of great interest.

However, it is noteworthy that the application of a hemadsorption filter does carry a significant cost and can lead to acute benzodiazepine withdrawal symptoms, as seen with flumazenil. Therefore, it should not be recommended for routine treatment of most patients admitted to ICU with this intoxication.

This report supports the use of a hemadsorption filter in slow metabolizers when the costs of a prolonged ICU admission could significantly outweigh those of applying a hemadsorption

filter. Cost effectiveness studies on this topic could be very interesting to determine the subset of patients in which we expect most benefit.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study protocol was reviewed and approved by the medical Ethics Committee UZ Brussel – VUB, approval number EC-2022-194.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The first draft of the manuscript was written by Michaël Mekeirele. The figures were created by Silke Verheyen. Michaël Mekeirele, Silke Verheyen, Ruth Van Lancker, Stephanie Wuyts, and Tim Balthazar all commented on previous versions of the manuscript.

Data Availability Statement

All relevant clinical data that were obtained for this case report are included in this article. Further inquiries can be directed to the corresponding author.

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